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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,852	01/17/2001	Kjell Olmarker	003300-712	9070

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EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/18/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/743,852	OLMARKER ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-58* is/are pending in the application.

4a) Of the above claim(s) *52-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-51 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *35-58* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1 & 9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 35-58 are pending in the instant application. Claim 35 has been amended and claim 58 has been added as requested by Applicant in Paper Number 12, filed August 30, 2002.

Claims 52-57 are withdrawn as being drawn to a non-elected invention.

Claims 35-51 and 58 are currently under examination.

Information Disclosure Statement

2. The IDSs filed Jan. 17, 2001 and June 28, 2002 have been considered.

Election/Restrictions

3. Applicant's assert that the finality of the restriction is in direct contradiction with PCT rules and with the guidelines set forth by the U.S. Patent and Trademark Office, and that according to M.P.E.P. § 1895.01(D), restriction practice under 35 U.S.C. 121, as it applies to national applications submitted under 35 U.S.C. 111(a) is not applicable to either international or national stage applications. Applicants' arguments have been fully considered but are not deemed persuasive because the restriction was determined under unity of invention principles set forth in 37 CFR 1.475 and 1.499. The two groups do not related to a single general concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical feature, because pharmaceutical compositions comprising TNF-α inhibitors were well known in the art and therefore cannot constitute a unifying technical feature.

The requirement is still deemed proper and remains FINAL.

Specification

4. The objections to the disclosure are withdrawn in view of Applicants' amendment.

Priority

5. Applicants' amendment to the specification for the priority statement is acknowledged, and a certified copy of the 9803276-6 application will be requested from the International Bureau if necessary.

Withdrawn Rejections

6.1 The provisional rejection of claims under obviousness-type double patenting is withdrawn in view of Applicants' terminal disclaimer.

6.2 The rejections of claims under 112 § 2 are withdrawn in view of Applicants' amendment.

Claim Objections

7. Claim 49 is objected to because of the following informalities: the term "is administered" is repeated in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 35-37 and 45-51 are rejected under 35 U.S.C. 102(e) as being anticipated by Amin et al., U.S. Patent No. 6,319,910, effective filing date Dec. 19, 1997.

Claims 35-37 and 45-51 encompass a method for inhibiting the action of TNF-α for treating nerve disorders in a mammal comprising administering a TNF-α inhibitor which may be a soluble cytokine receptor, a monoclonal antibody or a tetracycline or chemically modified tetracycline, that block TNF-α activity, wherein the mammal may be human, and wherein the TNF-α inhibitor is administered systemically, locally, parenterally, intramuscularly, intravenously by injection or infusion, subcutaneously, orally at a dosage of about 20 mg to about 1,500 mg, rectally, and wherein the tetracycline, which may be doxycycline, is administered at a dosage of about 100 mg.

Amin et al. teach that chemically modified tetracyclines, including doxycycline, are a class of non-steroidal anti-inflammatory drugs which inhibit TNF-α, and can be used for treating diseases or disorders associated with elevated activities of TNF-α (see abstract, column 3, line 55- column 4, line 2). Amin et al. also teach an effective amount of a chemically modified tetracycline used in a method for treating a disease or disorder associated with elevated levels of TNF-α, including neurodegenerative disorders (column 5, line 65 to column 6, line 24), that the invention is particularly useful in the treatment of humans, that the active principal may be administered by any means that achieves its intended purpose such as parenteral routes, subcutaneous, intravenous, intradermal, intramuscular, orally and other routes, and that the dosage administered will be dependent upon the age, sex, health and weight of the recipient, kind of concurrent treatment, frequency of treatment and nature of the effect desired, and that the most preferred dosage will be tailored to the individual subject, as is understood and determinable by one of skill in the art (column 6, line 41 to column 7, line 13), and the dosage may be 100mg (column 7, lines 33-44). Therefore, Amin et al. anticipates the claims.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 35-51 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amin et al., U.S. Patent No. 6,319,910, effective filing date Dec. 19, 1997, and further in view of Sommer et al., Neuroscience Letters, 237:45-48, 1997 (cited by Applicants).

Claims 35-51 and 58 encompass a method for inhibiting the action of TNF-α for treating nerve disorders which may involve pain in a mammal comprising administering a TNF-α inhibitor which may be a soluble cytokine receptor, a monoclonal antibody or a tetracycline or chemically modified tetracycline, that block TNF-α activity, wherein the mammal may be human, the nerve disorder is a spinal disorder which may be a nerve root injury and may be caused by herniated discs, or sciatica, or a nucleus pulposus-induced nerve injury, or spinal cord compression, and wherein the TNF-α inhibitor is administered systemically, locally, parenterally, intramuscularly, intravenously by injection or infusion, subcutaneously, orally at a dosage of about 20 mg to about 1,500 mg, rectally, and wherein the tetracycline, which may be doxycycline, is administered at a dosage of about 100 mg.

The teachings of Amin et al are described above. Amin et al. do not teach that the nerve disorder is a spinal disorder which may be a nerve root injury and may be caused by herniated discs, or sciatica, or a nucleus pulposus-induced nerve injury, or spinal cord compression.

Sommer et al. teach that inflammatory nerve pain from lepromatous leprosy is associated with a massive increase in the production of TNF, and that the pain can be dramatically reduced by inhibitors of TNF production. The reference also teaches that TNF levels are increased in experimental neuropathies, such as nerve crush, chronic constriction injury (CCI, a partial nerve injury), and experimental autoimmune neuritis, and that pharmacologic inhibition of TNF production reduces pain related behaviors in mice with CCI, and that neutralizing antibodies to TNF-α or other TNF-α inhibitors may have the same effect, (see columns 1 and 2, page 45). Sommer et al. also teach that the mature TNF-α is cleaved from the cell surface by a metalloprotease, and that use of the metalloprotease inhibitor TAPI blocks cleavage of the cell surface TNF and thus reduces levels of the mature TNF-α polypeptide in activated macrophages and T-cells, and describe experiments in mice in which ligatures were placed around the sciatic nerve and TAPI was administered by local epinerurial injection to the injured nerve. Pain was measured by two methods, withdrawal thresholds to heat to test for thermal hyperalgesia, and reaction to von Frey hairs to assess mechanical allodynia. Mice that were administered TAPI had reduced pain as measured by these methods (Fig. 1).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use the methods of treatment of Amin et al. to treat neurological conditions as described in Sommer et al. Since Sommer et al. teach that inflammatory nerve pain in a disease (lepromatous leprosy) and in experimental neuropathies results in increased levels of TNF-α, which can be reduced by TNF-α inhibitors, and since many nerve disorders such as spinal cord injury result in inflammation and increase in TNF-α, the skilled artisan would be motivated to treat any of these nerve disorders/injuries with the methods of Amin et al.

Although nucleus pulposus-induced nerve injury may not have been disclosed in the prior art, the method of treatment is inherently the same. Elucidation of an underlying mechanism does not make the method of treatment patently distinct. There would be a reasonable expectation of success, since TNF-α inhibitors have successfully been used to treat a large number of disorders that are associated with an increased TNF-α.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

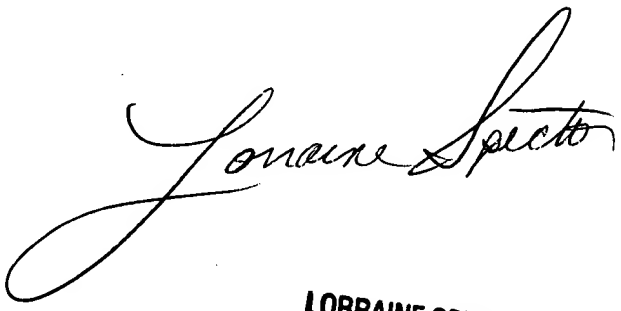
Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner



LORRAINE SPECTOR
PRIMARY EXAMINER